Recognizing and Managing Antiretroviral Treatment Failure (Last updated April 7, 2021; last reviewed April 7, 2021)

Panel's Recommendations

- The causes of antiretroviral (ARV) treatment failure—which include poor adherence, drug resistance, poor absorption of medications, inadequate dosing, and drug-drug interactions—should be assessed and addressed **(AII)**.
- Perform ARV drug-resistance testing when virologic failure occurs, while the patient is still taking the failing regimen **(AI*)** (see Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines for more information).
- ARV regimens should be chosen based on treatment history and drug-resistance testing, including both past and current resistance test results **(AI*)**.
- The new regimen should include at least two, but preferably three, fully active ARV medications; the assessment of anticipated ARV activity should be based on treatment history and past resistance test results **(AII*)**.
- The goal of therapy following treatment failure is to achieve and maintain virologic suppression, which is defined as a plasma viral load that is below the limits of detection as measured by highly sensitive assays with lower limits of quantification of 20 copies/mL to 75 copies/mL **(AI*)**.
- When complete virologic suppression cannot be achieved, the goals of therapy are to preserve or restore immunologic function (as measured by CD4 T lymphocyte values), prevent clinical disease progression, and prevent the development of additional drug resistance that could further limit future ARV drug options **(AII)**.
- Children who require evaluation and management of treatment failure should be managed by or in collaboration with a pediatric HIV specialist **(AI*)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Categories of Treatment Failure

Treatment failure can be categorized as virologic failure, immunologic failure, clinical failure, or some combination of the three. Immunologic failure refers to a suboptimal immunologic response to therapy or an immunologic decline while on therapy, but no standardized definition exists. Clinical failure is defined as the occurrence of new opportunistic infections (OIs) (excluding immune reconstitution inflammatory syndrome [IRIS]) and/or other clinical evidence of HIV disease progression during therapy. Almost all antiretroviral (ARV) management decisions for treatment failure are based on addressing virologic failure.

Virologic Failure

Virologic failure refers to either an incomplete initial response to therapy or a viral rebound after virologic suppression is achieved. *Virologic suppression* is defined as having plasma viral load below the lower level of detection, as measured by highly sensitive assays with lower limits of quantitation of 20 to 75 copies/mL. *Virologic failure* is defined as repeated instances of a plasma viral load ≥200 copies/mL after 6 months of therapy. Laboratory results must be confirmed with repeat testing before a final assessment of virologic failure is made.

Infants with high plasma viral loads at initiation of ART occasionally take longer than 6 months to achieve virologic suppression. Because of this, some experts continue the treatment regimen for infants if viral load is declining but is still ≥200 copies/mL at 6 months. These infants should be monitored closely until they achieve virologic suppression.[1] However, ongoing nonsuppression—especially with non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens—increases the risk of drug resistance.[2,3]

Controversy exists regarding the clinical implications of HIV RNA levels that are between the lower level of detection and <200 copies/mL in patients on antiretroviral therapy (ART). Adults with HIV who have detectable viral loads and a quantified result <200 copies/mL after 6 months of ART generally achieve virologic suppression without changing regimens.[4,5] However, some studies in adults have found that multiple viral load measurements of 50 copies/mL to <200 copies/mL (sometimes characterized as low-level viremia) may be associated with an increased risk of later virologic failure.[6–9] In contrast, a recent study followed a cohort of 57 adult patients with low-level viremia (21–200 copies/mL) reported that none of the patients were found to have resistance to their regimen, and all had adequate plasma ARV concentrations. At 96 weeks of follow-up, 67% remained with low-level viremia, 26% had viral loads <20 copies/mL, and only 7% had viral failure; none was attributed to viral resistance.[10]

"Blips"—defined as isolated episodes of a detectable but low level of plasma viral load (i.e., <500 copies/mL) that are followed by a return to viral suppression—are common and not generally reflective of short-term virologic failure, although they may indicate an increased risk of virologic failure after 12 months to 24 months.[11–13] However, repeated or persistent plasma viral loads that are ≥200 copies/mL (especially viral loads that are >500 copies/mL) in patients who have achieved virologic suppression usually indicate virologic failure.[5,13–15]

In a cohort of children from Cambodia, Indonesia, Malaysia, Thailand, and Vietnam, who were on first-line combination therapy,[16] among those who achieved viral suppression (<50 copies/mL on two successive measurements), 17% had at least one viral load with low-level viremia over a median follow-up of 6 years. More than a third of those had repeated episodes of low-level viremia. The rate of viral failure was 8.5 per 100 patient-years in those with low-level viremia versus 3.3 per 100 patient-years in those without low-level viremia. Of note, 97% of the cohort were started on an NNRTI-based regimen, which has a lower barrier to resistance than other regimens and, therefore, may not be generalizable to patients on other regimens.

Poor Immunologic Response Despite Virologic Suppression

Poor immunologic response despite virologic suppression is uncommon in children.[17] Patients with baseline severe immunosuppression (i.e., a CD4 T lymphocyte [CD4] cell count <500 cells/mm^3) often take longer than 1 year to achieve immune recovery, even if virologic suppression occurs more promptly. During this early treatment period of persistent immunosuppression, additional clinical disease progression can occur. In an international study, 12% of pediatric and adolescent patients had a poor immunologic response 1 year after viral suppression (defined as <400 copies/ml), although poor immunologic response dropped to 7% at 2 years and 3% at 3 years in those with continued viral suppression. Among those with a poor immunologic response at 1 year post viral suppression, a fourfold increased risk of an AIDS diagnosis or death was observed, compared with immune responders (rate ratio 4.04; 95% confidence interval, 1.83–8.92; $P < 0.001$).[18]

In cases of poor immunologic response despite virologic suppression, clinicians should first exclude laboratory error in CD4 values or viral load measurements and ensure that CD4 values have been interpreted correctly in relation to the natural decline in CD4 count that occurs during the first 5 to 6 years of life. Another laboratory consideration is that some viral load assays may not amplify all HIV groups and subtypes (e.g., HIV-1 non-M groups, HIV-2), resulting in falsely low or negative viral load results (see Diagnosis of HIV Infection in Infants and Children and Clinical and Laboratory Monitoring of Pediatric HIV Infection). Once laboratory results are confirmed, clinicians should evaluate patients for adverse events, medical conditions, and other factors that can cause CD4 values to decrease (see Table 17 below). Several drugs (e.g., corticosteroids, chemotherapeutic agents) and conditions (e.g., hepatitis C virus [HCV], tuberculosis [TB], malnutrition, Sjogren's syndrome, sarcoidosis, syphilis, cirrhosis, acute viral infections) are independently associated with low CD4 values.[19]

Patients who have very low baseline CD4 values before initiating ART are at higher risk of an impaired CD4 response to ART and, based on data from adult studies, may be at higher risk of death and AIDS-defining illnesses despite virologic suppression.[20-22] In a study of 933 children aged ≥5 years who received ART that resulted in virologic suppression, 348 children (37%) had CD4 counts <500 cells/mm^3 at ART initiation,

including 92 (9.9%) who had CD4 counts <200 cells/mm^3. After 1 year of virologic suppression, only seven children (1% of the cohort) failed to reach a CD4 count ≥200 cells/mm^3, and 86% of children had CD4 counts >500 cells/mm^3. AIDS-defining events were uncommon overall (occurring in 1% of participants), but they occurred both in children who did achieve improved CD4 counts and those who did not.[17] Several drugs (e.g., corticosteroids, chemotherapeutic agents) and conditions (e.g., hepatitis C virus [HCV], tuberculosis [TB], malnutrition, Sjogren's syndrome, sarcoidosis, syphilis, cirrhosis, acute viral infections) are independently associated with low CD4 values.[19]

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In summary, poor immunologic response to treatment can occur. Management consists of confirming that CD4 values and viral load measurements are accurate, avoiding the use of drugs that are associated with low CD4 values, and treating other conditions that could impair CD4 recovery. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does not recommend modifying an ARV regimen based on lack of immunologic response if virologic suppression is confirmed.

Poor Clinical Response Despite Adequate Virologic and Immunologic Responses

Clinicians must carefully evaluate patients who experience clinical disease progression despite favorable immunologic and virologic responses to ART; not all of these cases represent ART failure. At times, after initiation of ART, patients will suffer a clinical deterioration due to paradoxical worsening of a known OI, or unmasking of a previously undiagnosed OI due to a profound immune response (IRIS) related to successful viral suppression. This does not represent ART treatment failure and does not generally require discontinuation of, or a change in ART. IRIS does not mean that ART has failed, and it does not generally require discontinuation of ART.[24,25] Children who have suffered irreversible damage to their lungs, brain, or other organs—especially during prolonged and profound pretreatment immunosuppression—may continue to have recurrent infections or symptoms in the damaged organs because the immunologic improvement may not reverse damage to the organs.[26] Such cases do not represent ART failure, and these children would not benefit from a change in ARV regimen. Before a definitive conclusion of ART clinical failure is reached, a child should also be evaluated to rule out (and, when indicated, treat) other causes or conditions that can occur with or without HIV-related immunosuppression, such as pulmonary TB, malnutrition, and malignancy.

Occasionally, however, children will develop new HIV-related OIs (e.g., *Pneumocystis jirovecii* pneumonia or esophageal candidiasis that occurs more than 6 months after achieving markedly improved CD4 values and virologic suppression) that are not related to IRIS, pre-existing organ damage, or another cause.[17] Although such cases are rare, they may represent ART clinical failure, and improvement in CD4 values may not necessarily normalize immunologic function. In children who have signs of new or progressive abnormal neurodevelopment, some experts change the ARV regimen, aiming to include agents that are known to achieve higher concentrations in the central nervous system; however, the data regarding the effectiveness of this strategy are inconclusive.[27,28]

Table 17. Discordance Among Virologic, Immunologic, and Clinical Responses

Differential Diagnosis of Poor Immunologic Response Despite Virologic Suppression
Poor Immunologic Response Despite Virologic Suppression and Good Clinical Response:
• Laboratory error (in CD4 value or viral load measurement)
• Misinterpretation of normal, age-related CD4 count decline (i.e., the immunologic response is not actually poor)
• Low pretreatment CD4 count or percentage
• Adverse effects (AEs) that are associated with the use of certain drugs (e.g., ZDV, TMP-SMX, systemic corticosteroids)
• Use of systemic corticosteroids or chemotherapeutic agents
• Conditions that can cause low CD4 values (e.g., HCV, acute viral infections, TB, malnutrition, Sjogren's syndrome, sarcoidosis, syphilis)
Poor Immunologic and Clinical Responses Despite Virologic Suppression:
• Labratory error (in CD4 value or viral load measurement)
• Falsely low viral load result for an HIV strain/type that is not detected by viral load assay (i.e., HIV-1 non-M groups, HIV-1 non-B subtypes, HIV-2 [although this is unusual with newer viral load assays])
• Persistent immunodeficiency that occurs soon after initiating ART but before ART-related reconstitution
• Primary protein-calorie malnutrition
• Untreated TB
• Malignancy
Differential Diagnosis of Poor Clinical Response Despite Adequate Virologic and Immunologic Responses
• IRIS
• A previously unrecognized, pre-existing infection or condition (e.g., TB, malignancy)
• Malnutrition
• Clinical manifestations of previous organ damage: brain (e.g., strokes, vasculopathy, worsening neurodevelopmental delay), lungs (e.g., bronchiectasis), cardiac (i.e., cardiomyopathy), renal (i.e., HIV-related kidney disease)
• A new clinical event due to a non-HIV illness or condition
• A new, otherwise unexplained, HIV-related clinical event (e.g., treatment failure)

Key: AE = adverse effects; ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; HCV = hepatitis C virus; IRIS = immune reconstitution inflammatory syndrome; TB = tuberculosis; TMP-SMX = trimethoprim-sulfamethoxazole; ZDV = zidovudine

Management of Virologic Failure

The approach to managing and subsequently treating virologic failure will differ, depending on the etiology of the problem. When assessing a child with suspected virologic failure, clinicians should evaluate therapy adherence and medication intolerance, confirm that the prescribed dosing is correct (and understood by the child and/or caregiver) for all medications in the regimen, consider possible pharmacokinetic (PK) interactions that might lead to low drug levels, and test for possible drug resistance (see Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines). Although many factors can contribute to virologic failure, the main barrier to sustained virologic suppression in adults and children is incomplete adherence to medication regimens, with subsequent emergence of viral mutations that confer partial or complete resistance to one or more components of the ARV regimen. See Adherence to Antiretroviral Therapy in Children and Adolescents Living with HIV for guidance on assessing adherence and strategies for improving adherence.

Virologic Failure with No Antiretroviral Drug Resistance Identified

Persistent viremia in the absence of detectable viral resistance to current medications is usually a result of nonadherence, but it is important to exclude other factors, such as poor drug absorption, incorrect dosing, and drug interactions. If adequate drug exposure can be ensured, then adherence to the current regimen should result in virologic suppression. Resistance testing should take place while a child is on therapy. After discontinuing therapy, plasma viral strains may quickly revert to wild type and reemerge as the predominant viral population, in which case, resistance testing can fail to identify the drug-resistant virus (see Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines). In this situation, resistance can be identified by restarting the prior medications while emphasizing adherence and repeating resistance testing in 4 weeks if plasma virus remains detectable. If the HIV plasma viral load becomes undetectable, then nonadherence was likely the original cause of virologic failure.

Virologic failure of boosted PI-based regimens is frequently associated with no detected major PI resistance mutations.[29] Virologic suppression may be achieved by continuing the PI-based regimen, implementing adherence-improvement measures, and addressing any PI-related side effects.[30–32] However, continued virologic failure on PI-based regimens, especially if PI drug levels are subtherapeutic or in the presence of nucleoside reverse transcriptase inhibitors (NRTI) resistance mutations, can lead to major PI mutations.[33]

In some cases, if a new, more convenient regimen could address the main barrier to adherence, it may be reasonable for a clinician to switch a patient to this new regimen (e.g., a single fixed-dose combination [FDC] tablet taken once daily) while closely monitoring adherence and viral load. Similarly, if an ART side effect or tolerability is found to be impacting adherence, switching to a new regimen with close monitoring should be considered. However, in cases where clinicians determine that patients have poor adherence to the current regimen and that adherence is unlikely to improve with a new regimen, clinicians should focus on improving adherence before initiating a new regimen (see Adherence to Antiretroviral Therapy in Children and Adolescents with HIV).

Virologic Treatment Failure with Antiretroviral Drug Resistance Identified

After deciding that a change in therapy is necessary, a clinician should attempt to identify at least two, but preferably three, fully active ARV agents from at least two different drug classes to use in a patient's new regimen. The clinician should consider all of the patient's past and recent drug-resistance test results, the patient's prior exposure to ARV drugs, whether the patient is likely to adhere to the regimen, and whether the patient finds a particular regimen acceptable.[34-38] This process often requires using agents from one or more drug classes that are new to the patient. However, clinicians should be aware that drug-resistance mutations can confer cross-resistance within a drug class, so a drug that is new to the patient may still have diminished antiviral potency. Substituting or adding a single drug to a failing regimen **is not recommended**, because this is unlikely to lead to durable virologic suppression and will likely result in additional drug resistance.

The process of switching a patient to a new regimen must include an extensive discussion of treatment adherence and potential toxicity with the patient and the patient's caregivers. This discussion should be appropriate for the patient's age and stage of development. Clinicians should be aware that some medications have conflicting food requirements of and concomitant medication restrictions that may complicate the administration of a regimen. Timing of medication administration is particularly important, because it helps ensure adequate ARV drug exposures throughout the day. Palatability, pill size, number of pills, and dosing frequency all need to be considered when choosing a new regimen.[39]

Therapeutic Options to Achieve Complete Virologic Suppression After Virologic Failure

A pediatric HIV specialist should be consulted when determining which new regimen will have the best chance of achieving complete virologic suppression in children who have already experienced treatment failure.

ARV regimens should be chosen based on a patient's treatment history and drug-resistance test results to optimize ARV drug potency in the new regimen. A general strategy for regimen changes is shown in Table 18; however, as additional agents are licensed and studied for use in children, newer regimens that are better tailored to the needs of each patient may be constructed.

Data from adult and pediatric studies support the efficacy of regimen that contains a boosted PI plus two NRTIs for those who experience treatment failure on an initial NNRTI-based regimen.[40] Studies of adults have found that a regimen that contains both a boosted PI and raltegravir (RAL) produces similar outcomes to a regimen that contains a boosted PI and two NRTIs.[40,41]

A clinical trial in adults who had experienced treatment failure on an initial NNRTI-based regimen reported that dolutegravir (DTG) had better efficacy and a better safety profile than lopinavir/ritonavir (LPV/r) when these drugs were used in second-line regimens that included at least one active NRTI.[42] Pediatric and adolescent data support the use of two NRTIs plus an INSTI, following the failure of an NNRTI-based regimen.[43-45]

However, caution should be exercised when considering the use of regimens that include first-generation INSTIs with a lower barrier to resistance (e.g., RAL), because children who experience treatment failure on

NNRTI-based regimens often have substantial NRTI resistance.[46]

Resistance to the NNRTI nevirapine (NVP) results in cross-resistance to the NNRTI efavirenz (EFV), and vice versa. The NNRTIs etravirine (ETR) and rilpivirine (RPV) can retain activity against NVP-resistant virus or EFV-resistant virus in the absence of certain key NNRTI mutations (see below), but ETR has generally been tested only in regimens that also contain a boosted PI.[34,37] For this reason, the Panel recommends using ETR as part of a regimen that includes a ritonavir (RTV)-boosted PI, see Etravirine section.

If a child experiences virologic failure on an initial PI-based regimen, there are often limited resistance mutations detected, indicating that poor adherence/tolerance of the regimen may be the cause of poor viral control.[46,48] In these cases, an alternative PI that might be potent and better tolerated can be used. For example, LPV/r-based regimens have been shown to have durable ARV activity in some PI-experienced children.[49-51] Darunavir/ritonavir-based therapy has also been used.[52,53] Switching to an INSTI-based regimen can also be effective in some PI-experienced children.[43,45,54-56] When making the switch from a failing PI-based regimen to an INSTI-based regimen, preference might be given to the second-generation INSTIs DTG or bictegravir (BIC), as these drugs have a higher barrier to resistance than the first-generation INSTIs RAL and elvitegravir.[57]

The availability of newer drugs within existing drug classes and the introduction of new classes of drugs increase the likelihood of finding three active drugs, even for children with extensive drug resistance (see Table 18). As previously discussed, INSTI-based regimens are increasingly used for children who have experienced treatment failure on NNRTI-based regimens or PI-based regimens.[43,45] RAL is the INSTI that has been studied and used most often in children, but both DTG and BIC are appealing for their once-daily administration, small pill size, and higher barrier to development of drug resistance; they also retain ARV activity in patients who have experienced treatment failure on RAL-based therapy (see the Dolutegravir and Bictegravir sections for the latest age/weight indications).[58] The use of DTG around the time of conception has been associated with a very small significant increase in the risk of infant neural tube defects (NTDs) that should be considered and addressed in counseling for adolescents of childbearing potential and their caregivers. For additional information, see the Dolutegravir section and refer to the Perinatal Guidelines (see Teratogenicity, Recommendations for Use of Antiretroviral Drugs During Pregnancy, and Appendix C. Antiretroviral Counseling Guide for Health Care Providers).

Maraviroc, a CCR5 antagonist, provides a new drug class, but many ART-experienced children already harbor CXCR4-tropic virus, which precludes its use.[59] Regimens that include an INSTI and a potent, boosted PI with or without ETR have been effective during small studies of extensively ART-experienced patients with multiclass drug resistance.[60–63] It is important to review individual drug profiles for information about drug interactions and dose adjustments when devising a regimen for children with multiclass drug resistance. Appendix A: Pediatric Antiretroviral Drug Information provides detailed information on drug formulations, pediatric and adult doses, and toxicity, as well as discussions of the available data on the use of ARV drugs in children.

Previously prescribed drugs that were discontinued because of poor tolerance or poor adherence may sometimes be reintroduced if drug resistance did not develop and if prior difficulties with tolerance and adherence can be overcome (e.g., by switching to a new formulation, such as an FDC tablet).

Some studies in adults have suggested that lamuvidine (3TC) can still contribute to suppression of HIV replication in patients with 3TC resistance mutations. Continuation of 3TC can also maintain a 3TC mutation (184V) that can partially reverse the effects of other mutations that confer resistance to zidovudine and tenofovir disoproxil fumarate.[64–66]

Studies have compared the use of NRTI-sparing and NRTI-containing regimens in adults with multidrug resistance who experienced virologic failure on a previous regimen. These studies have demonstrated no clear benefit of including NRTIs in the new regimen.[67,68] One of these studies reported no difference in rate of virologic suppression but a trend towards a higher mortality in adults who were randomized to receive a regimen that included NRTIs than in adults who were randomized to receive an NRTI-sparing regimen.[68] There are no studies of NRTI-sparing regimens in children with virologic failure and multidrug resistance, but an NRTI-sparing

regimen may be a reasonable option for children with extensive NRTI resistance.

Enfuvirtide (T-20) is approved by the Food and Drug Administration (FDA) for use in ART-experienced children aged ≥6 years, but it must be administered by subcutaneous injection twice daily.[69,70] Regimens that contain more than three drugs (up to three PIs and/or two NNRTIs) have shown efficacy in a pediatric case series, but they are complex, often poorly tolerated, and subject to unfavorable drug-drug interactions.[71] The availability of agents with an increased barrier to resistance, such as the PI darunavir, the second-generation NNRTIs ETR and RPV, and newer INSTIs (DTG,BIC), have lessened the need for T-20, dual-PI regimens, and regimens of four or more drugs.

The FDA has recently granted approval for two novel agents that inhibit the attachment of the gp120 region of the virus to the CD4 molecule. Oral fostemsavir is a gp120 attachment inhibitor, and ibalizumab (given by infusion twice monthly) is a humanized monoclonal antibody that targets the gp120 attachment area on the CD4 molecule. Both are approved for adolescents ≥18 years with multidrug resistance.[72,73] As these represent drugs with new novel targets, they would be expected to be beneficial in patients with multiclass drug resistance.

When searching for at least two fully active agents in cases of extensive drug resistance, clinicians should consider the potential availability of new therapeutic agents that are not currently being studied in children or that may be approved for use in children in the future. Information about clinical trials can be found using the National Institute of Allergy and Infectious Diseases (NIAID) database and by consulting a pediatric HIV specialist. Children should be enrolled in clinical trials of new drugs whenever possible.

The use of new drugs that have been evaluated in adults but have not been fully evaluated in children may be justified; ideally, this would be done in the framework of a clinical trial. Expanded access programs or clinical trials may be available (see ClinicalTrials.gov). New drugs should be used in combination with at least one, but ideally two, additional active agents.

Pediatric dosing for off-label use of ARV drugs is problematic, because absorption, hepatic metabolism, and excretion change with age.[74] In clinical trials of several ARV agents, direct extrapolation of a pediatric dose from an adult dose, based on a child's body weight or body surface area, was shown to result in an underestimation of the appropriate pediatric dose.[75]

Off-label use of ARV agents, however, may be necessary for children with HIV who have limited ARV drug options. In this circumstance, consulting a pediatric HIV specialist for advice about potential regimens, assistance with access to unpublished data from clinical trials or other limited off-label pediatric use, and referral to suitable clinical trials are recommended.

Management Options When Two Fully Active Agents Cannot Be Identified or Administered

It may be impossible to provide an effective and sustainable therapeutic regimen because no combination of currently available agents is active against extensively drug-resistant virus in a patient or because a patient is unable to adhere to or tolerate ART.

The decision to continue a nonsuppressive regimen must be made on an individual basis after weighing potential benefits and risks. Specifically, providers must balance the inherent tension between the benefits of virologic suppression and the risks of continued viral replication with potential evolution of viral drug resistance in the setting of inadequate ARV drug exposure (e.g., nonadherence or a nonsuppressive, suboptimal regimen). Nonsuppressive regimens could decrease viral fitness and thus, slow clinical and immunologic deterioration while a patient is either working on adherence or awaiting access to new agents that are expected to achieve sustained virologic suppression.[76] However, persistent viremia in the context of ARV drug pressure has the potential to generate additional resistance mutations that could further compromise agents in the same class that might otherwise have been active in subsequent regimens (e.g., continuing first-generation INSTIs or NNRTIs). Patients who continue to use nonsuppressive regimens should be followed more closely than those with stable virologic status, and the potential to successfully initiate a fully suppressive ART regimen

should be reassessed at every opportunity.

The use of NRTI-only holding regimens or a complete interruption of therapy **are not recommended**. One trial (IMPAACT P1094) randomized children with the M184V resistance mutation and documented nonadherence to continue their nonsuppressive, non-NNRTI-based regimen or to switch to a 3TC (or emtricitabine [FTC]) monotherapy-holding regimen. Children who switched to monotherapy were significantly more likely to experience a 30% decline in absolute CD4 count (the primary outcome) over a 28-week period. Only patients in the 3TC/FTC arm experienced the primary outcome.[77]

Complete treatment interruption has also been associated with immunologic declines and poor clinical outcomes, and it **is not recommended** (see Considerations About Interruptions in Antiretroviral Therapy).[78,79]

Table 18. Options for Regimens with at Least Two Fully Active Agents to Achieve Virologic Suppression in Patients with Virologic Failure and Evidence of Viral Resistance (page 1 of 2)

To optimize ARV drug effectiveness, clinicians should evaluate a patient's treatment history and drug-resistance test results when choosing an ARV regimen. Doing so is particularly important when selecting the NRTI components of an NNRTI-based regimen, where drug resistance to the NNRTI can occur rapidly if the virus is not sufficiently sensitive to the NRTIs. Regimens should contain at least two, but preferably three, fully active drugs for durable and potent virologic suppression. If the M184V/I mutation associated with FTC and 3TC is present, these medications should be continued if the new regimen contains TDF, TAF, or ZDV. The presence of this mutation may increase susceptibility to these NRTIs.

Please see individual drug profiles for information about age limitations (e.g., do not use DRV in children aged <3 years), drug interactions, and dose adjustments when devising a regimen for children with multiclass drug resistance. Collaboration with a pediatric HIV specialist is especially important when choosing regimens for children with multiclass drug resistance. Regimens in this table are provided as examples, but the list is not exhaustive.

Prior Regimen	New Regimen Options[a]
Two NRTIs plus an NNRTI	Two NRTIs plus a boosted PI Two NRTIs plus an INSTI[b]
Two NRTIs plus a PI	Two NRTIs plus an INSTI[b] Two NRTIs plus a different boosted PI INSTI plus a different boosted PI with or without an NNRTI and with or without NRTI(s) Two NRTIs plus an NNRTI[c]
Two NRTIs plus an INSTI	Two NRTIs plus a boosted PI DTG[a,b] or BIC[b] (if not used in the prior regimen) with a boosted PI with or without one or two NRTIs. DTG must be given twice daily if a patient has certain documented INSTI mutations, or if there is concern about certain mutations (see the Dolutegravir section). Two NRTIs plus an NNRTI[c]
Failed Regimen(s) That Included NRTI(s), NNRTI(s), and PI(s)	**If NRTIs Are Fully Active** • INSTI plus two NRTIs **If NRTIs Are Not Fully Active** • INSTI plus two NRTIs with or without an RTV-boosted PI **If There Is Minimal NRTI Activity** • INSTI with or without an RTV-boosted PI with or without ETR, or RPV with or without NRTI(s) • Consider adding T-20 and/or MVC if additional active drug(s) are needed.

Prior Regimen	New Regimen Options[a]
Failed Regimen(s) That Included NRTI(s), NNRTI(s), and PI(s) continued	• Consider off-label use of approved agents or enrollment in clinical trials for novel antiretroviral treatments

[a] Exposure to DTG around the time of conception has been associated with a very small significant increase in the risk of infant NTDs that should be addressed in counseling for adolescents of childbearing potential and their caregivers. For additional information, refer to the Perinatal Guidelines (see Teratogenicity, Recommendations for Use of Antiretroviral Drugs During Pregnancy, and Appendix C. Antiretroviral Counseling Guide for Health Care Providers).

[b] RAL has a low barrier to resistance and requires twice-daily dosing in children and adolescents; BIC and DTG have a higher barrier to resistance and only require once-daily dosing. Many Panel members would use BIC/FTC/TAF (Biktarvy) in patients with prior treatment failure who have virus with the M184 mutation, see Bictegravir section.

[c] NNRTI could be an option in younger patients with no exposure to NNRTIs and taste aversion to boosted PIs.

Key: 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; DRV = darunavir; DTG = dolutegravir; ETR = etravirine; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

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